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(54) Title: HETEROCYCLIC DERIVATIVES AS INHIBITORS OF FACTOR XA

(57) Abstract: The invention relates to pharmaceutically-acceptable salts of 1-(5-chloroindol-2-yluslfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine and reduced particle sized forms of either the compound or a pharmaceutically-acceptable salt thereof, which possess antithrombotic and anticoagulant properties and accordingly are useful in mehtods of treatment of humans or animals. The invention also relates to processes for the preparation of pharmaceutically-acceptable salts of the above compound and reduced particle size forms thereof, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect in humans.

HETEROCYCLIC DERIVATIVES AS INHIBITORS OF FACTOR XA

The invention relates to pharmaceutically-acceptable salts of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine and reduced particle sized forms of either the compound or a pharmaceutically-acceptable salt thereof, which possess antithrombotic and anticoagulant properties and accordingly are useful in methods of treatment of humans or animals. The invention also relates to processes for the preparation of pharmaceutically-acceptable salts of the above compound and reduced particle size forms thereof, to pharmaceutical compositions containing them and to their use in the manufacture of medicaments for use in the production of an antithrombotic or anticoagulant effect in humans.

The antithrombotic and anticoagulant effect produced by the compound of the invention is believed to be attributable to their strong inhibitory effect against the activated coagulation protease known as Factor Xa. Factor Xa is one of a cascade of proteases involved in the complex process of blood coagulation. The protease known as thrombin is the final protease in the cascade and Factor Xa is the preceding protease which cleaves prothrombin to generate thrombin.

Certain compounds are known to possess Factor Xa inhibitory properties and the field has been reviewed by R.B. Wallis, Current Opinion in Therapeutic Patents, 1993, 1173-1179. Thus it is known that two proteins, one known as antistatin and the other known as tick anticoagulant protein (TAP), are specific Factor Xa inhibitors which possess antithrombotic properties in various animal models of thrombotic disease.

It is also known that certain non-peptidic compounds possess Factor Xa inhibitory properties. Of the low molecular weight inhibitors mentioned in the review by R.B. Wallis, all possessed a strongly basic group such as an amidinophenyl or amidinonaphthyl group.

We have now found that 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine (hereinafter referred to as Compound 1) possesses Factor Xa inhibitory activity at

concentrations which do not inhibit, or which inhibit to a lesser extent, the enzyme thrombin which is also a member of the blood coagulation enzymatic cascade.

Compound 1 is disclosed as Example 3 of WO9957113.

Compound 1 possesses activity in the treatment or prevention of a variety of medical disorders where anticoagulant therapy is indicated, for example in the treatment or prevention of thrombotic conditions such as coronary artery and cerebro-vascular disease. Further examples of such medical disorders include various cardiovascular and cerebrovascular conditions such as myocardial infarction, the formation of atherosclerotic plaques, venous or arterial thrombosis, coagulation syndromes, vascular injury (including reocclusion and restenosis following angioplasty and coronary artery bypass surgery, thrombus formation after the application of blood vessel operative techniques or after general surgery such as hip replacement surgery, the introduction of artificial heart valves or on the recirculation of blood), cerebral infarction, cerebral thrombosis, stroke, cerebral embolism, pulmonary embolism, ischaemia and angina (including unstable angina).

Compound 1 is also useful as an inhibitor of blood coagulation in an ex-vivo situation such as, for example, the storage of whole blood or other biological samples suspected to contain Factor Xa and in which coagulation is detrimental.

Compound 1, i.e. the free base, has limited aqueous solubility and hence limited bioavailabilty when dosed orally. We have investigated pharmaceutically-acceptable salts of Compound 1 and also solid forms of pharmaceutically-acceptable salts of Compound 1 with reduced particle size.

Accordingly provided in the present invention is:

(a) a reduced particle size form of a pharmaceutically-acceptable salt or a solvate thereof of Compound 1;

(b) a reduced particle size form of Compound 1 or a solvate thereof; and

(c) a pharmaceutically-acceptable salt of Compound 1 or a solvate thereof.

As used hereinafter the term "a Compound of the invention" refers to either one of features (a), (b) or (c) described above.

By the use of the term "reduced particle size" we refer to solid Compound 1, or a pharmaceutically-acceptable salt thereof, or a solvate of either thereof, reduced by suitable processing techniques to a solid of smaller particle size and, consequently, greater surface area. Any number of processing techniques known in the pharmaceutical field may be used to reduce solid particle size, such as grinding, milling and micronising, reference should be made to Remington: The Science and Practise of Pharmacy, 19th Ed., pages 1598-1602, for a more exhaustive review.

The range of particle sizes preferred in this invention are, in increasing preference, moderately fine powder, fine powder, very fine powder, microfine powder to, most preferably, superfine powder.

The above reference to particle sizes are taken from the British Pharmacopoeia 1993, Volume II, Appendix XVII B, A193, and are reproduced below for reference.

Moderately fine powder

A powder all the particles of which pass through a sieve with a nominal mesh aperture of 355μm and not more than 40.0% by weight pass through a sieve with a nominal mesh aperture of 250μm.

Fine powder

A powder all the particles of which pass through a sieve with a nominal mesh aperture of 180μm and not more than 40.0% by weight pass through a sieve with a nominal mesh aperture of 125μm.

Very fine powder

A powder all the particles of which pass through a sieve with a nominal mesh aperture of 125μm and not more than 40.0% by weight pass through a sieve with a nominal mesh aperture of 45μm.

Microfine powder

A powder of which not less than 90% by weight of the particles pass through a sieve with a nominal mesh aperture of 45μm.

Superfine powder

A powder of which not less than 90% by weight of the particles pass through a sieve with a nominal mesh aperture of 10μm.

The particular sieves to be used in determining the particle size are described in British Pharmacopoeia 1993 Volume II, Appendix XVIIB, A193-A194, which part thereof is incorporated herein by reference.

Pharmaceutically-acceptable salts may be formed by reacting the basic moiety of Compound 1 with any one of a number of pharmaceutically-acceptable organic or inorganic acids and, preferably, precipitating the salt from solution. A preferred pharmaceutically-acceptable salt of Compound 1 is the methane sulphonate salt.

A feature of the invention is a Compound of the invention, as described above, for use in medical therapy.

According to a further feature of the invention there is provided a pharmaceutical composition which comprises a Compound of the invention, as described above, in association with a pharmaceutically-acceptable diluent or carrier.

The composition may be in a form suitable for oral use, for example a tablet, capsule, aqueous or oily solution, suspension or emulsion; for topical use, for example a

cream, ointment, gel or aqueous or oily solution or suspension; for nasal use, for example a snuff, nasal spray or nasal drops; for vaginal or rectal use, for example a suppository; for administration by inhalation, for example as a finely divided powder such as a dry powder, a microcrystalline form or a liquid aerosol; for sub-lingual or buccal use, for example a tablet or capsule; or for parenteral use (including intravenous, subcutaneous, intramuscular, intravascular or infusion), for example a sterile aqueous or oily solution or suspension. In general the above compositions may be prepared in a conventional manner by intimately mixing a Compound of the invention with suitable excipient(s).

The amount of a Compound of the invention, as described above that is combined with one or more excipients to produce a single dosage form will necessarily vary depending upon the host treated and the particular route of administration. For example, a formulation intended for oral administration to humans will generally contain, for example, from 0.5 mg to 2 g of Compound of the invention (active ingredient) compounded with an appropriate and convenient amount of excipient(s) which may vary from about 5 to about 98 percent by weight of the total composition. Dosage unit forms will generally contain about 1 mg to about 500 mg of an active ingredient.

The invention also includes the use of a Compound of the invention, as described above in the production of a medicament for use in:-

(i) producing a Factor Xa inhibitory effect;

(ii) producing an anticoagulant effect;

(iii) producing an antithrombotic effect;

(iv) treating a Factor Xa mediated disease or medical condition;

(v) treating a thrombosis mediated disease or medical condition;

(vi) treating coagulation disorders; and/or

(vii) treating thrombosis or embolism involving Factor Xa mediated coagulation.

The invention also includes a method of producing an effect as defined hereinbefore or treating a disease or disorder as defined hereinbefore which comprises

administering to a warm-blooded animal, preferably a human, requiring such treatment an effective amount of form of a Compound of the invention, as described above.

The size of the dose for therapeutic or prophylactic purposes of a Compound of the invention, as described above, will naturally vary according to the nature and severity of the medical condition, the age and sex of the animal or patient being treated and the route of administration, according to well known principles of medicine. In using a Compound of the invention it will generally be administered so that a daily oral dose in the range, for example, 0.1 to 50 mg/kg body weight/day is received, given if required in divided doses. In general lower doses will be administered when a parenteral route is employed, for example a dose for intravenous administration in the range, for example, 0.01 to 10 mg/kg body weight/day will generally be used. Preferred oral daily doses include, for example, 0.1 to 10 mg/kg body weight/day. In general a preferred dose range for either oral or parenteral administration would be 0.01 to 10 mg/kg body weight/day.

Compound 1 may conveniently be prepared by coupling (4-pyridyl)benzoic acid, or a reactive derivative thereof, for example the acylchloride derivative, with 1-(5-chloroindol-2-ylsulfonyl)piperazine, or a salt thereof, for example, the hydrochloride salt. The reaction is conveniently carried out in the presence of a suitable base such as, for example, an alkali or alkaline earth metal carbonate, alkoxide, hydroxide or hydride, for example sodium carbonate, potassium carbonate, sodium ethoxide, potassium butoxide, sodium hydroxide, potassium hydroxide, sodium hydride or potassium hydride, or an organometallic base such as an alkyl-lithium, for example n-butyl-lithium, or a dialkylamino-lithium, for example lithium di-isopropylamide, or, for example, an organic amine base such as, for example, pyridine, 2,6-lutidine, collidine, 4-dimethylaminopyridine, triethylamine, morpholine or diazabicyclo[5.4.0]undec-7-ene. The reaction is also preferably carried out in a suitable inert solvent or diluent, for example methylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran, 1,2-dimethoxyethane, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidin-2-one, dimethylsulphoxide or acetone, and at a temperature in the range, for example, -78° to 150°C, conveniently at or near ambient temperature.

Processes for the preparation of the two intermediates above, as well as for Compound 1, may be found in PCT application number WO9957113.

Compound 1 or a Compound of the invention may be administered as a sole therapy or they may be administered in conjunction with other pharmacologically active agents such as a thrombolytic agent, for example tissue plasminogen activator or derivatives thereof or streptokinase. The compounds of the invention may also be administered with, for example, a known platelet aggregation inhibitor (for example aspirin, a thromboxane antagonist or a thromboxane synthase inhibitor), a known hypolipidaemic agent or a known anti-hypertensive agent.

The dissolution rates of material were tested in analogous methods as described in the British Pharmacopoeia 1998 Appendix XIID A189-A191.

The invention will now be illustrated in the following Examples.

Example 1

Preparation of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine) methane sulfonate salt from free base:

To a stirred suspension of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine) free base (55g of 92% strength, 0.105 mol) in a mixture of dichloromethane (750ml) and methanol (250ml) was added in portions a solution of methane sulfonic acid (6.8 ml, 0.105 mol, 1 eq.) in distilled water (20 ml). The resulting suspension was stirred for one hour, by which time a complete solution was obtained. This was evaporated *in vacuo*, with addition of extra methanol to displace water and dichloromethane.

The resulting solid mass was suspended in refluxing methanol (800 ml), and distilled water added portionwise until complete solution was achieved. The hot solution was treated with charcoal for approx. 30 minutes, and then filtered. The volume was reduced *in vacuo* to approx. 200 ml, and the total volume then made up to 350 ml by addition of methanol. The solution was left to stand at 0 °C overnight and the solid filtered off. This was dried at 80 °C

for 16hrs and then at 85 °C for a further 16 hours to give 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine) methane sulfonate salt as a colourless solid, (42g).

^{1}H NMR (d_6-DMSO) δ = 2.3 ppm (s, 3H), δ = 3.0 - 3.3 ppm (broad s, 4H), δ = 3.4 - 3.9 ppm (broad d, 4H), δ = 7.0 ppm (s, 1H), δ = 7.35 ppm (d, 1H), δ = 7.5 ppm (d, 1H), δ = 7.6 ppm (d, 2H), δ = 7.8 ppm (s, 1H), δ = 8.0 ppm (d, 2H), δ = 8.35 ppm (d, 2H), δ = 8.95 ppm (d, 2H), δ = 12.4 ppm (s, 1H), the spectrum also contained a signal due to methanol (<0.1 mol eq.);

MS $(M+H)^+$ 481/483;

Microanalysis

found: C, 51.2, 51.1; H, 4.3, 4.3; N, 9.5, 9.4; Cl, 6.2, 5.9; S, 11.0, 11.0; H_2O, 0.9, 0.9 %;

$C_{24}H_{21}N_4O_3ClS$. 1.0 CH_3SO_3H. 0.33 H_2O. 0.12 CH_4O

requires: C, 51.4; H, 4.5; N, 9.6; Cl, 6.0; S, 10.9; H_2O, 1.0 %;

mp 250-253 °C.

Example 2

Preparation of Reduced Particle Size Form

Traditional techniques in reducing particle size may be used such as micronisation, such as by feeding the compound or salt at a controlled rate into a fluid energy mill (microniser), in which the compound or salt is subjected to self attrition caused by high energy streams of gas. The particles produced are then continuously classified, with the fines collected via a filter.

Example 3

Illustrative pharmaceutical dosage forms suitable for presenting a Compound of the invention for therapeutic or prophylactic use include the following tablet and capsule formulations, which may be obtained by conventional procedures well known in the art of pharmacy and are suitable for therapeutic use in humans:

(a) Tablet I	mg/tablet
Compound Z*	1.0
Lactose Ph. Eur.	93.25
Croscarmellose sodium	4.0
Maize starch paste (5% w/v aqueous paste)	0.75
Magnesium Stearate	1.0

(b) Tablet II	mg/tablet
Compound Z*	50
Lactose Ph. Eur	223.75
Croscarmellose sodium	6.0
Maize starch	15.0
Polyvinylpyrrolidone (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

(c) Tablet III	mg/tablet
Compound Z*	100
Lactose Ph. Eur.	182.75
Croscarmellose sodium	12.0
Maize starch paste (5% w/v aqueous paste)	2.25
Magnesium stearate	3.0

(d) Capsule	mg/capsule
Compound Z*	10
Lactose Ph. Eur.	488.5
Magnesium stearate	1.5

Note

* The active ingredient Compound Z is a Compound of the invention, as described above.

The tablet compositions (a)-(c) may be enteric coated by conventional means, for example, with cellulose acetate phthalate.

CLAIMS

1. A reduced particle size form of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine or a solvate thereof.

2. A reduced particle size form of a pharmaceutically-acceptable salt or a solvate thereof of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine.

3. A pharmaceutically-acceptable salt of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine or a solvate thereof.

4. A reduced particle size form as claimed in either claim 1 or 2 which is a moderately fine powder as defined in the British Pharmacopoeia 1993.

5. A reduced particle size form as claimed in either claim 1 or 2 which is a fine powder as defined in the British Pharmacopoeia 1993.

6. A reduced particle size form as claimed in either claim 1 or 2 which is a very fine powder as defined in the British Pharmacopoeia 1993.

7. A reduced particle size form as claimed in either claim 1 or 2 which is a microfine powder, as defined in the British Pharmacopoeia 1993.

8. A reduced particle size form as claimed in either claim 1 or 2 which is a superfine powder, as defined in the British Pharmacopoeia 1993.

9. 1-(5-Chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine) methane sulfonate salt.

10. A pharmaceutical composition which comprises a pharmaceutically-acceptable salt of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine or a solvate thereof or

a reduced particle size form of 1-(5-chloroindol-2-ylsulfonyl)-4-[4-(4-pyridyl)benzoyl] piperazine, or a pharmaceutically-acceptable salt thereof or a solvate of either thereof, in association with a pharmaceutically-acceptable diluent or carrier.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 00/02770

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D401/12 A61K31/4439 A61P7/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WALLIS R B: "INHIBITORS OF COAGULATION FACTOR XA: FROM MACROMOLECULAR BEGINNINGS TO SMALL MOLECULES" CURRENT OPINION IN THERAPEUTIC PATENTS, 1 August 1993 (1993-08-01), pages 1173-1179, XP000653726 ISSN: 0962-2594 cited in the application the whole document	1-3,9,10
X,P	WO 99 57113 A (CAULKETT PETER WILLIAM RODNEY ;PEARSON STUART ERIC (GB); WALKER RO) 11 November 1999 (1999-11-11) page 12, line 6 - line 8; claims 1,13,16-18; example 3	1-3,9,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
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Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 21188 A (TURNER PAUL ;PRESTON JOHN (GB); STOCKER ANDREW (GB); ZENECA LTD (G) 22 May 1998 (1998-05-22) claims 1,15-17; example 12	1-3,9,10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 00/02770

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9957113 A	11-11-1999	AU 3620699 A	23-11-1999
WO 9821188 A	22-05-1998	AU 4874897 A	03-06-1998
		BR 9712672 A	26-10-1999
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		CZ 9901634 A	11-08-1999
		EP 0937048 A	25-08-1999
		NO 992230 A	07-05-1999
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		SK 61399 A	14-02-2000